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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/530,483 | 09/28/2005 | Joerg Rosenberg | 268305US0PCT | 5340 |

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| EXAMINER | |
|---|---|
| SASAN, ARADHANA | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1615 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) |
|---|---|---|
| | 10/530,483 | ROSENBERG ET AL. |
| | Examiner | Art Unit |
| | Aradhana Sasan | 1615 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *06 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/6/05 and 12/22/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application*

1. Claims 1-9 are included in the prosecution.

### *Priority*

2. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).

### *Information Disclosure Statement*

3. The information disclosure statements (IDS) submitted on 4/6/2005 and 12/22/05 are acknowledged. The submissions are in compliance with the provisions of 37 CFR 1.97 and 1.98. Accordingly, the examiner is considering the information disclosure statements.

See attached copy of PTO-1449.

### *Claim Rejections - 35 USC § 103*

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vladyka et al. (US 2002/0012706 A1) in view of Thacharodi et al. (EP 0 960 620 A1).

The claimed invention is a process for producing solid dosage forms where a moldable composition is formed. The composition comprises 50 to 99.4% b weight of at least one crosslinked nonthermoplastic carrier, 0.5 to 30% by weight of at least one

adjuvant (selected from the group consisting of thermoplastic polymers, lipids, sugar alcohols, sugar alcohol derivatives and solubilizers) and 0.1 to 49.5% by weight of at least one active ingredient. The moldable composition is formed at a temperature at or above the softening point of the adjuvant, at least at 70°C, and subsequently cooled.

Vladyka teaches a method that "involves melting a normally solid hydrophobic vehicle, ... dissolving therein a sparingly water-soluble, normally crystalline ... pharmaceutically active agent at a temperature above the normal melting temperature of the vehicle but below the normal melting or degradation temperature of active agent, then granulating the molten product with a disintegrant and optional additives" (Page 1, [0011]). The granulation is cooled and the "resulting granular particles may then be milled to an appropriate particle size, and filled into capsules, or blended with other excipients and processed into solid dosage forms" (Page 1, [0011]). The formulations have the advantage of "improved solubility and bioavailability" (Page 2, [0014]). A solid hydrophobic vehicle that is capable of dissolving the pharmaceutically active agent and having a melting point above about 60°C and selected from glyceryl monostearate, monoglycerides, diglycerides, and waxes are disclosed (Page 2, [0017]). The hydrophobic vehicle is used in the range of from about 3% to about 55% by dry weight of the granular formulation (Page 2, [0017]). Stabilizers (selected from sorbitol, mannitol, polyvinylpyrrolidone and hydroxypropylmethylcellulose or HPMC) used in the range of about 1% to about 60% by weight of the dry granulation are disclosed (Page 2, [0019]). Disintegrants (selected from croscarmellose sodium and crospovidone) used in the range from about 1% to about 25% by dry weight of the formulation are disclosed

(Page 3, [0021]). The active agent comprises from 20% to about 35% of the granular particle (Page 3, [0026]). Example 6 discloses the process where the active itraconzole (32.6%) was added to molten glyceryl monostearate (5.5%); the mixture was heated until all of the active ingredient was completely dissolved. HPMC (48.9%) and croscarmellose sodium (13%) were mixed in a high shear granulator and the molten mixture of glyceryl monostearate and the active was mixed and granulated. The granulated mixture was rapidly cooled to solidify the granulate (Pages 5-6, [0054]). The reference teaches that: "if the particles of the final granulation are undesirably large, it is suitable to grind them and screen them to a more acceptable, more uniform size" (Page 4, [0045]). It is also disclosed that: "Granules that are produced by this invention may be placed directly into hard gelatin capsules to create the final dosage form. ... If ... it is desired to compress the granules into tablets using a tableting machine, the addition of a lubricant may be necessary to prevent the processing problems associated with this operation" (Page 4, [0046]).

Vladyka does not expressly teach the percentages of the crosslinked nonthermoplastic carrier and the thermoplastic polymer.

Thacharodi teaches a process for making a pharmaceutical composition which comprises "mixing together a substituted pyridylsulfinyl benzimidazole ... with a pharmaceutically acceptable carrier, the carrier comprising at least one polymer which is at least partially comprised of vinylpyrrolidone monomeric units, together with any optionally included pharmaceutically acceptable excipients" (Page 3, [0012]). The pharmaceutically acceptable carrier is present in an amount from about 10% to about

98% by weight of the total weight of the composition (Page 5, [0020]). Fatty acid glycerides may also be used as pharmaceutically acceptable carriers (Page 5, [0022]). The fatty acid glyceride is "heated to above its melting point and the liquid obtained [is] mixed with other ingredients of the composition to obtain granules" (Page 5, [0023]). Example 6 discloses the heating of fatty acid glycerides (AKOMED R at 13.33% and GELUCIRE at 6.67%) to 60°C. After cooling the fatty acid glycerides to 30°C, a blend of the active ingredient (omeprazole at 13.33%) and cross-linked polyvinylpyrrolidone (KOLLIDON CL-M at 66.67%) was granulated with the fatty acid glycerides (Page 7, [0037] and Table 7).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of making a granular pharmaceutical vehicle by melting a hydrophobic vehicle, dissolving a sparingly water-soluble pharmaceutically active agent, and granulating the molten product, as suggested by Vladyka, combine it with the process of making a granular pharmaceutical composition with a high percentage (10 to 98%) of a pharmaceutically acceptable carrier, as taught by Thacharodi, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Thacharodi teaches a process where a high level of cross-linked polyvinylpyrrolidone (KOLLIDON CL-M at 66.67%) is used in a stable oral pharmaceutical composition (Page 7, [0037], Table 7 and Page 8, Tables 9 and 10).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed

invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Regarding instant claim 1, the limitation of a process for producing solid dosage forms would have been obvious to one skilled in the art over the process of making granular forms for use in capsules or tablets as taught by Vladyka (Page 4, [0046]). The limitation of a moldable composition which is formed at or above the softening point of the adjuvant, but at least at 70°C and subsequently cooled would have been obvious over the process disclosed in Example 6 by Vladyka (Pages 5-6, [0054]). The limitation of "at least at 70°C" would have been obvious to one skilled in the art because Vladyka teaches "a temperature above the normal melting temperature of the vehicle but below the normal melting or degradation temperature of active agent" is used in the process (Page 1, [0011]). Therefore, one skilled in the art would melt the hydrophobic vehicle and the melting point would vary depending on the particular hydrophobic vehicle chosen. The percentage (50 to 99.4%) of the crosslinked nonthermoplastic carrier would have been obvious over the cross-linked polyvinylpyrrolidone (KOLLIDON CL-M) used at 66.67% in Example 6 by Thacharodi (Page 7, [0037] and Table 7). The percentage (0.5 to 30%) of adjuvant would have been obvious over the 5.5% of glyceryl monostearate (lipid) taught by Vladyka (Pages 5-6, Example 6, [0054]). The percentage (0.1 to 49.5%) of active ingredient would have been obvious over the 32.6% of active (itraconzole) taught by Vladyka (Pages 5-6, Example 6, [0054]) and 13.33% of active (omeprazole at 13.33%) taught by Thacharodi (Page 7, [0037] and Table 7).

Regarding instant claim 2, the limitation of 50 to 90% of at least one crosslinked nonthermoplastic carrier would have been obvious to one skilled in the art over the cross-linked polyvinylpyrrolidone (KOLLIDON CL-M) used at 66.67% in Example 6 by Thacharodi (Page 7, [0037] and Table 7). The limitation of 5 to 30% of a thermoplastic carrier would have been obvious over the pharmaceutically acceptable carrier (present in an amount from about 10% to about 98%) comprising at least one polymer which is at least partially comprised of vinylpyrrolidone monomeric units, as taught by Thacharodi (Page 3, [0012]). The limitation of 0.5 to 20% of a solubilizer would be obvious over the solubilizers AKOMED R (caprylic/capric triglyceride at 13.33%) and GELUCIRE (glycerol esters of $C_8$-$C_{18}$ fatty acids at 6.67%) as taught by Thacharodi (Page 7, [0037] and Table 7). The limitation of 0.1 to 45.5% of an active ingredient would have been obvious over the 32.6% of active (itraconzole) taught by Vladyka (Pages 5-6, Example 6, [0054]) and 13.33% of active (omeprazole at 13.33%) taught by Thacharodi (Page 7, [0037] and Table 7).

Regarding instant claim 3, the crosslinked nonthermoplastic carrier would have been obvious over the cross-linked polyvinylpyrrolidone (KOLLIDON CL-M) used in Example 6 by Thacharodi (Page 7, [0037] and Table 7).

Regarding instant claim 4, the thermoplastic polymer would have been obvious over the polymer which is at least partially comprised of vinylpyrrolidone monomeric units, as taught by Thacharodi (Page 3, [0012]).

Regarding instant claim 5, the sugar alcohol would have been obvious over the sorbitol and mannitol taught by Vladyka (Page 2, [0019]).

Regarding instant claim 6, the lipid would have been obvious over the glyceryl monostearate (lipid) taught by Vladyka (Pages 5-6, Example 6, [0054]).

Regarding instant claim 7, the solubilizer would have been obvious over the solubilizers AKOMED R (caprylic/capric triglyceride at 13.33%) and GELUCIRE (glycerol esters of $C_8$-$C_{18}$ fatty acids at 6.67%) taught by Thacharodi (Page 7, [0037] and Table 7).

Regarding instant claim 8, the active ingredient with a solubility in water at 25°C of less than 1mg/ml would have been obvious over the sparingly water-soluble pharmaceutically active agent taught by Vladyka (Page 1, [0011]).

Regarding instant claim 9, the limitation of the cooled composition that is comminuted and compressed into the dosage form would have been obvious over the grinding of the granules to an acceptable size and compressing the granules into tablets, as taught by Vladyka (Page 4, [0045] and [0046]).

***Conclusion***

6. No claims are allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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